Appendix A. Search Strategy

RTI MDD Search Strategy

Pubmed 02.05.2014

Search	Query	Items found
#1	Search ("Bupropion"[Mesh] OR "Bupropion"[tiab] OR 34911-55-2[rn])	3570
#2	Search ("Citalopram"[Mesh] OR "Citalopram"[tiab] OR 59729-33-8[rn])	5061
#3	Search (“Escitalopram”[tiab] OR 128196-01-0[rn])	4031
#4	Search ("O-desmethylvenlafaxine" [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn])	234
#5	Search ("Fluoxetine"[Mesh] OR "Fluoxetine"[tiab] OR 54910-89-3[rn])	10911
#6	Search ("Fluvoxamine"[Mesh] OR "Fluvoxamine"[tiab] OR 54739-18-3[rn])	2551
#7	Search (("milnacipran"[Supplementary Concept] OR “Levomilnacipran”[tiab] OR 96847-54-0[rn]))	346
#8	Search ("mirtazapine"[Supplementary Concept] OR "mirtazapine"[tiab] OR 85650-52-8[rn])	1574
#9	Search ("nefazodone"[Supplementary Concept] OR "nefazodone"[tiab] OR 82752-99-6[rn])	706
#10	Search ("Paroxetine"[Mesh] OR "Paroxetine"[tiab] OR 61869-08-7[rn])	5220
#11	Search ("Sertraline"[Mesh] OR "Sertraline"[tiab] OR 79617-96-2[rn])	3732
#12	Search ("Trazodone"[Mesh] OR "Trazodone"[tiab] OR 19794-93-5[rn])	1685
#13	Search ("venlafaxine"[Supplementary Concept] OR "venlafaxine"[tiab] OR 93413-69-5[rn])	3124
#14	Search ("vilazodone"[Supplementary Concept] OR "vilazodone"[tiab] OR 163521-12-8[rn])	65
#15	Search ("vortioxetine"[Supplementary Concept] OR "vortioxetine"[tiab] OR 508233-74-7[rn])	50
#16	Search ("Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Second-Generation"[Pharmacological Action])	57579
#17	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	67046
#18	Search ("Psychotherapy"[Mesh] OR psychotherap*[tiab])	156412
#19	Search (Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab])	8028
#20	Search (#18 OR #19)	158665
#21	Search "Hypericum"[Mesh] OR “Hypericum“[tiab] OR “St. Johns Wort”[tiab] OR “Saint Johns Wort”[tiab] OR “St. John’s Wort”[tiab] OR “Saint John’s Wort”[tiab] OR LI160[tiab] OR LI160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab]	2591
#22	Search “s adenosyl l methionine”[tiab] OR “s adenosylmethionine”[tiab] OR "S-Adenosylmethionine"[Mesh]	8814
#23	Search “Fatty Acids, Omega-3"[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab]	27732
#24	Search "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab]	20337
#25	Search "Yoga"[Mesh] OR yoga[tiab]	2387
#26	Search "Meditation"[Mesh] OR meditation[tiab] OR mindfulness[tiab]	4174
#27	Search (“Exercise“[Mesh] OR physical activit*[tiab] OR "physical exercise"[tiab])	159734
#28	Search (#22 OR #23 OR #24 OR #25 OR #26 OR #27)	221143
#29	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35489
#30	Search (#29 AND (#28 OR #20 OR #17))	7950
#31	Search (systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND	241160

Search	Query	Items found
	(bibliographic*[tiab] OR literature[tiab])) OR “research synthesis”[tiab] OR “research integration”[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR “meta-analysis as topic”[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab])	
#32	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial”[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	542163
#33	Search (("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab]))	349594
#34	Search ("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab])	319105
#35	Search (#30 AND (#31 OR #32 OR #33 OR #34))	3642
#36	Search ("Animals"[Mesh] NOT "Humans"[Mesh])	3882887
#37	Search (#35 NOT #36)	3635
#38	Search ("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]	1490657
#39	Search (#37 NOT #38)	3398
#40	Search #39 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la])	3231

Addendum duloxetine 07.05.2014

Search	Query	Items found
#1	Search ("duloxetine" [Supplementary Concept] OR duloxetine[tiab])	1677
#2	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35518
#3	Search (#1 AND #2)	430
#4	Search ((systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “research synthesis”[tiab] OR “research integration”[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR “meta-analysis as topic”[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab]))	241577
#5	Search (("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial”[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	542686
#6	Search ((("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab])))	349872
#7	Search (("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab]))	319351
#8	Search (#3 AND (#7 OR #6 OR #5 OR #4))	234
#9	Search (("Animals"[Mesh] NOT "Humans"[Mesh]))	3884483
#10	Search (#8 NOT #9)	234
#11	Search (("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])	1491426
#12	Search (#10 NOT #11)	234
#13	Search (#12 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la]))	229

Cochrane Library 02.05.2014

ID	Search	Hits
#1	[mh Bupropion] or "Bupropion":ti,ab	934
#2	[mh Citalopram] or "Citalopram":ti,ab	1196
#3	Escitalopram:ti,ab	588
#4	Desvenlafaxine:ti,ab	71
#5	[mh Fluoxetine] or "Fluoxetine":ti,ab	2364
#6	[mh Fluvoxamine] or "Fluvoxamine":ti,ab	687
#7	Levomilnacipran:ti,ab	12
#8	mirtazapine:ti,ab	439
#9	nefazodone:ti,ab	194
#10	[mh Paroxetine] or "Paroxetine":ti,ab	1770
#11	[mh Sertraline] or "Sertraline":ti,ab	1350
#12	[mh Trazodone] or "Trazodone":ti,ab	335
#13	venlafaxine:ti,ab	989
#14	vilazodone:ti,ab	19
#15	vortioxetine:ti,ab	13
#16	[mh "Antidepressive Agents, Second-Generation"]	1230
#17	{or #1-#16}	9063
#18	[mh Psychotherapy] or psychotherap*:ti,ab	17066
#19	(Acceptance near/2 Commitment next Therap*):ti,ab or (Cognitive near/2 Therap*):ti,ab or ((interpersonal or psychodynamic or behavioral) next therap*):ti,ab	5015
#20	#18 or #19	19087
#21	[mh yoga] or yoga:ti,ab	688
#22	[mh meditation] or (meditation or mindfulness):ti,ab	1064
#23	[mh Acupuncture] or [mh "Acupuncture Therapy"] or (Acupuncture or Electroacupuncture):ti,ab	7130
#24	[mh Hypericum] or "Hypericum":ti,ab or (john* next wort):ti,ab or (LI160 or WS5572 or WS5573 or LoHyp-57):ti,ab	295
#25	("s adenosyl l methionine" or "s adenosylmethionine"):ti,ab or [mh S-Adenosylmethionine]	191
#26	[mh "fatty Acids, Omega-3"] or (omega-3 and fatty next acid*):ti,ab or ("fish oil" or "flax seed" or "borage seed" or Borago or "evening primrose" or Oenothera or "eicosapentaenoic acid" or PUFA):ti,ab	3661
#27	[mh Exercise] or (physical next (activit* or exercise)):ti,ab	18551
#28	{or #21-#27}	31146
#29	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#30	#29 and (#17 or #20 or #28)	3544
#31	#30 Publication Date from 1990 to 2014	3460
#32	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#33	#31 not #32	2867
#34	#31 and (adult or adults):ti,ab	393
#35	#33 or #34	2945
#36	[mh animals] not [mh humans]	5655
#37	#35 not #36 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2940
#38	(review:pt and systematic:ti,ab) or "systematic review"	37971
#39	meta-analysis:pt or (meta next analy*):ti,ab or metaanaly*:ti,ab or [mh Meta-Analysis] or [mh "Meta-Analysis as Topic"]	20924
#40	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#41	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149716
#42	([mh "cohort studies"] or (cohort next stud*):ti,ab or [mh "case-control studies"] or (case-control next stud*):ti,ab or (observational next stud*):ti,ab or "observational study":pt or ((observational or longitudinal or retrospective) near/2 (study or trial)):ti,ab) and ("comparative study":pt or [mh "Comparative Study"] or comparison:ti,ab or	51743

ID	Search	Hits
	comparative:ti,ab)	
#43	{or #38-#42}	458686
#44	#37 and #43 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2000

Addendum duloxetine 07.05.2014

No.	Query	Results
#30	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#31	#30 and "duloxetine":ti,ab	163
#32	#31 Publication Date from 1990 to 2014	163
#33	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#34	#32 not #33	143
#35	#32 and (adult or adults):ti,ab	29
#36	#34 or #35	149
#37	[mh animals] not [mh humans]	5655
#38	#36 not #37 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	149
#39	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#40	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149722
#41	#38 and (#39 or #40) in Trials	87
#42	#38 in Other Reviews	8
#43	#42 or #41	95

EMBASE 06.05.2014

No.	Query	Results
#1.1	'amfebutamone'/exp OR bupropion:tn,ab,ti OR '34911 55 2':rn	
#1.2	'citalopram'/exp OR citalopram:tn,ab,ti OR '59729 33 8':rn OR 'escitalopram'/exp OR escitalopram:tn,ab,ti OR '128196 01 0':rn	
#1.3	'desvenlafaxine'/exp OR desvenlafaxine:tn,ab,ti OR '93413 62 8':rn	
#1.4	'fluoxetine'/exp OR fluoxetine:tn,ab,ti OR '54910 89 3':rn	
#1.5	'fluvoxamine'/exp OR fluvoxamine:tn,ab,ti OR '54739 18 3':rn	
#1.6	'milnacipran'/exp OR levomilnacipran:tn,ab,ti OR '96847 54 0':rn	
#1.7	'mirtazapine'/exp OR mirtazapine:tn,ab,ti OR '85650 52 8':rn	
#1.8	'nefazodone'/exp OR nefazodone:tn,ab,ti OR '82752 99 6':rn	
#1.9	'paroxetine'/exp OR paroxetine:tn,ab,ti OR '61869 08 7':rn	
#1.10	'sertraline'/exp OR sertraline:tn,ab,ti OR '79617 96 2':rn	
#1.11	'trazodone'/exp OR trazodone:tn,ab,ti OR '19794 93 5':rn	
#1.12	'venlafaxine'/exp OR venlafaxine:tn,ab,ti OR '93413 69 5':rn	
#1.13	'vilazodone'/exp OR vilazodone:tn,ab,ti OR '163521 12 8':rn	
#1.14	'vortioxetine'/exp OR vortioxetine:tn,ab,ti OR '508233 74 7':rn	
#1.15	'antidepressant agent'/exp AND 'second generation':ab,ti	
#1.16	#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15	87062
#1.17	'psychotherapy'/exp	187201
#1.18	((acceptance OR cognitive OR interpersonal OR psychodynamic OR behavioral) NEXT/3 (therapy OR therapies OR psychotherapy)):ab,ti	20374
#1.19	#1.17 OR #1.18 AND 'treatment outcome'/exp	25169
#1.20	'hypericum'/exp OR hypericum:ab,ti OR (john* NEXT/1 wort):ab,ti OR li160:ab,ti OR ws5572:ab,ti OR ws5573:ab,ti OR 'lohyp 57':ab,ti	4193
#1.21	's adenosylmethionine'/exp OR 's adenosylmethionine' OR 's adenosyl l methionine':ab,ti OR 's adenosylmethionine':ab,ti	10557

No.	Query	Results
#1.22	'omega 3 fatty acid'/exp OR ('omega 3':ab,ti AND acid*:ab,ti) OR 'fish oil':ab,ti OR 'flax seed':ab,ti OR 'borage seed':ab,ti OR borago:ab,ti OR 'evening primrose':ab,ti OR oenothera:ab,ti OR 'eicosapentaenoic acid':ab,ti OR pufa:ab,ti	34034
#1.23	'acupuncture'/exp OR acupuncture:ab,ti OR electroacupuncture:ab,ti	33369
#1.24	'yoga'/exp OR yoga:ab,ti	4138
#1.25	'meditation'/exp OR meditation:ab,ti OR mindfulness:ab,ti	6584
#1.26	'exercise'/exp	209232
#1.27	#1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25 OR #1.26 AND 'treatment outcome'/exp	19807
#1.28	'major depression'/exp OR 'major depressive disorder':ab,ti OR (major NEXT/2 depress*):ab,ti	52013
#1.29	#1.28 AND (#1.27 OR #1.19 OR #1.16)	13000
#1.30	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti)) OR (review:it AND review:ab,ti AND (rationale:ab,ti OR evidence:ab,ti))	287380
#1.31	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#1.32	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#1.33	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#1.34	#1.29 AND (#1.30 OR #1.31 OR #1.32 OR #1.33)	
#1.35	'human'/exp	14753345
#1.36	#1.34 AND #1.35	4575
#1.37	'adult'/exp	5294678
#1.38	#1.36 AND #1.37	2399
#1.39	#1.38 AND [1990-2014]/py	2374
#1.40	#1.39 AND [english]/lim	2316
#1.41	#1.39 AND (german:la OR italian:la)	17
#1.42	#1.40 OR #1.41	2333
#1		2333
#2	#1 AND [embase]/lim	2232

Addendum duloxetine 07.05.2014

No.	Query	Results
#6	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#7	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#8	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#9	#5 OR #6 OR #7 OR #8	1017694
#10	#4 AND #9	582
#11	#10 AND 'human'/exp AND 'adult'/exp	210
#12	#11 AND [1990-2014]/py AND [embase]/lim	205
#13	#12 AND ([english]/lim OR german:la OR italian:la)	205

CINAHL (via Ebsco) 02.05.2014

#	Query	Results
S1	(MH "Bupropion") OR "Bupropion"	1,072
S2	(MH "Citalopram") OR "Citalopram"	644
S3	"Escitalopram"	202
S4	(MH "Desvenlafaxine Succinate") OR TX Desvenlafaxine	49
S5	(MH "Fluoxetine+") OR "Fluoxetine"	1,144
S6	(MH "Fluvoxamine Maleate") OR "Fluvoxamine"	145
S7	"Levomilnacipran"	5
S8	(MH "Mirtazapine") OR "mirtazapine"	255
S9	(MH "Nefazodone") OR "nefazodone"	68
S10	(MH "Paroxetine") OR "Paroxetine"	732
S11	(MH "Sertraline Hydrochloride") OR "Sertraline"	643
S12	(MH "Trazodone") OR "Trazodone"	168
S13	(MH "Venlafaxine+") OR "venlafaxine"	605
S14	"vilazodone"	11
S15	"vortioxetine"	5
S16	(MH "Antidepressive Agents, Second Generation+")	2,806
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	4,599
S18	(MH "Psychotherapy+") OR (TI psychotherap*) OR (AB psychotherap*)	86,97
S19	TI (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*) OR AB (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*)	4,172
S20	S18 OR S19	87,95
S21	(MH "Yoga+") OR (TI yoga) OR (AB yoga)	2,268
S22	(MH "Meditation") OR (TI (meditation OR mindfulness)) OR (AB (meditation OR mindfulness))	2,652
S23	(MH "St. John's Wort") OR "hypericum" OR (TI john* N2 wort) OR (AB john* N2 wort) OR (TI (LI160 OR WS5572 OR WS5573 OR LoHyp-57)) OR (AB (LI160 OR WS5572 OR WS5573 OR LoHyp-57))	932
S24	(MH "Fatty Acids, Omega-3+") OR (TI "omega 3" N1 fatty acid*) OR (AB "omega 3" N1 fatty acid*) OR (TI ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)) OR (AB ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA))	4,996
S25	(MH "S-Adenosylmethionine") OR (TI (“s adenosyl l methionine” OR “s adenosylmethionine”)) OR (AB (“s adenosyl l methionine” OR “s adenosylmethionine”))	204
S26	(MH "Acupuncture+") OR (TI (acupuncture OR electroacupuncture)) OR (AB (acupuncture OR electroacupuncture))	8,556
S27	(MH "Exercise+") OR TI (physical N1 (activit* OR exercise)) OR AB (physical N1 (activit* OR exercise))	65,646
S28	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	83,353
S29	(MH "Depression+") AND (TX major N2 depress*)	3,393
S30	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	3,998
S31	S29 OR S30	4,08
S32	S31 AND (S17 OR S20 OR S28)	1,115
S33	(MH "Animals") NOT (MH "Human")	24,505
S34	S32 NOT S33	1,114
S35	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,397
S36	S34 NOT S35	1,012
S37	S36 AND (PY 1990-2014) AND (LA (english OR german Or italian))	1,003
S38	S37 NOT (PT (editorial OR letter OR commentary))	867

Addendum duloxetine 07.05.2014

#	Query	Results
S1	(MH "Duloxetine Hydrochloride") OR (TX Duloxetine)	378
S2	(MH "Depression+") AND (TX major N2 depress*)	3,397
S3	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	4
S4	S2 OR S3	4,082
S5	S4 AND S1	51
S6	(MH "Animals") NOT (MH "Human")	24,582
S7	S5 NOT S6	51
S8	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,684
S9	S7 NOT S8	51
S10	S9 AND (PY 1990-2014) AND (LA (english OR german Or italian))	51
S11	S10 NOT (PT (editorial OR letter OR commentary))	50

AMED (via Ovid) 02.05.2014

#	Suchen	Ergebnisse
1	exp antidepressive agents/	272
2	Bupropion.mp.	15
3	Citalopram.mp.	9
4	Escitalopram.mp.	3
5	(Desvenlafaxine or O-desmethylvenlafaxine).mp.	0
6	Fluoxetine.mp.	50
7	Levomilnacipran.mp.	0
8	mirtazapine.mp.	6
9	(nefazodone or Paroxetine or Sertraline or Trazodone or venlafaxine or vilazodone or vortioxetine).mp.	69
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	363
11	exp psychotherapy/	8542
12	((acceptance or cognitive or interpersonal or psychodynamic or behavioral) adj3 (therap$ or psychotherap$)).mp.	1395
13	11 or 12	8895
14	exp fatty acids/ or exp fish oils/ or (omega 3 and acid*).mp. or (flax seed or borage seed or Borago or evening primrose or Oenothera or eicosapentaenoic acid or PUFA).mp.	640
15	exp hypericum/ or (hypericum or (john$ adj1 wort)).mp. or (LI160 or WS5572 or WS5573 or LoHyp-57).mp.	415
16	(S-Adenosylmethionine or s adenosyl l methionine).mp.	21
17	exp acupuncture/ or exp electroacupuncture/ or (acupuncture or electroacupuncture).mp.	9182
18	exp meditation/ or (meditation or mindfulness).mp.	658
19	exp Yoga/ or yoga.mp.	501
20	(physical adj1 (activit* or exercise)).mp. or exp Exercise/	9857
21	14 or 15 or 16 or 17 or 18 or 19 or 20	20984
22	exp depressive disorder/	890
23	((major adj2 depress$) or major depressive disorder).mp.	352
24	22 or 23	1126
25	10 or 13 or 21	29843
26	24 and 25	283
27	26	283
28	limit 27 to yr="1990 -Current"	282
29	(exp infant/ or exp child/ or exp adolescent/) not exp adult/	15352
30	28 not 29	269
31	28 and (adult or adults).ti,ab.	39
32	30 or 31	271

Addendum duloxetine 07.05.2014

#	Suchen	Ergebnisse
1	duloxetine.mp.	22
2	exp depressive disorder/	894
3	((major adj2 depress$) or major depressive disorder).mp.	353
4	2 or 3	1131
5	1 and 4	5

PsycInfo (via Ebsco) 02.05.2014

#	Query	Results
S1	TX (Bupropion OR Citalopram OR Escitalopram OR O-desmethylvenlafaxine OR Desvenlafaxine OR Fluoxetine OR Fluvoxamine OR Levomilnacipran OR mirtazapine OR nefazodone OR Paroxetine OR Sertraline OR Trazodone OR venlafaxine OR vilazodone OR vortioxetine)	15,857
S2	DE "antidepressant drugs" AND TX (second generation)	144
S3	S1 OR S2	15,958
S4	(DE "acceptance and commitment therapy") or ((DE "cognitive therapy") or (DE "behavior therapy")) OR (DE psychotherapy)	64,196
S5	TI ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*)) OR AB ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*))	24,311
S6	S4 OR S5	78,648
S7	(DE acupuncture) OR (TX (acupuncture OR electroacupuncture))	1,717
S8	(DE meditation) OR (TX (meditation OR mindfulness))	8,986
S9	(DE hypericum perforatum) OR (TX (hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57))	392
S10	(DE yoga) OR (TX yoga)	1,907
S11	TX ((omega-3 N1 fatty acid*) OR "fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)	982
S12	TX (“s adenosyl l methionine” OR “s adenosylmethionine”)	205
S13	DE exercise OR TI physical activit* OR AB physical activit*	30,086
S14	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	43,124
S15	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,026
S16	S15 AND (S3 OR S6 OR S14)	13,953
S17	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S18	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S19	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S20	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S21	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731
S22	(S17 OR S18 OR S19 OR S20 OR S21) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S23	S16 AND S22	3,595
S24	((ZP "animal")) not ((ZP "human"))	279,088

#	Query	Results
S25	S23 NOT S24	3,586
S26	(((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)"))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S27	S25 NOT S26	3,4
S28	LA (english OR german OR italian)	3,441,047
S29	PY 1990-2014	2,451,294
S30	S27 AND S28 AND S29	3,172

Addendum duloxetine 07.05.2014

#	Query	Results
S1	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,027
S2	S1 AND (TX duloxetine)	375
S3	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S4	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S5	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S6	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S7	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731
S8	(S3 OR S4 OR S5 OR S6 OR S7) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S9	S2 AND S8	161
S10	((ZP "animal")) not ((ZP "human"))	279,088
S11	S9 NOT S10	161
S12	(((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)"))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S13	S11 NOT S12	161
S14	LA (english OR german OR italian)	3,441,047
S15	PY 1990-2014	2,451,294
S16	S13 AND S14 AND S15	154

Grey Literature Search

ClinicalTrials.gov 04.06.2014

41 studies found for:
("major depressive disorder" OR "major depression") AND Bupropion Adult, Senior Phase 2, 3, 4
170 studies found for:
("major depressive disorder" OR "major depression") AND Citalopram Adult, Senior Phase 2, 3, 4
170 studies found for:
("major depressive disorder" OR "major depression") AND Escitalopram Adult, Senior Phase 2, 3, 4
35 studies found for:
("major depressive disorder" OR "major depression") AND Desvenlafaxine Adult, Senior Phase 2, 3, 4
45 studies found for:
("major depressive disorder" OR "major depression") AND Fluoxetine Adult, Senior Phase 2, 3, 4
6 studies found for:
("major depressive disorder" OR "major depression") AND Fluvoxamine Adult, Senior Phase 2, 3, 4
7 studies found for:
("major depressive disorder" OR "major depression") AND Levomilnacipran Adult, Senior Phase 2, 3, 4
21 studies found for:
("major depressive disorder" OR "major depression") AND mirtazapine Adult, Senior Phase 2, 3, 4

Found no studies with search of: ("major depressive disorder" OR "major depression") AND nefazodone Adult, Senior Phase 2, 3, 4
61 studies found for:
("major depressive disorder" OR "major depression") AND Paroxetine Adult, Senior Phase 2, 3, 4
66 studies found for:
("major depressive disorder" OR "major depression") AND Sertraline Adult, Senior Phase 2, 3, 4
4 studies found for:
("major depressive disorder" OR "major depression") AND Trazodone Adult, Senior Phase 2, 3, 4
66 studies found for:
("major depressive disorder" OR "major depression") AND venlafaxine Adult, Senior Phase 2, 3, 4
13 studies found for:
("major depressive disorder" OR "major depression") AND vilazodone Adult, Senior Phase 2, 3, 4
24 studies found for:
("major depressive disorder" OR "major depression") AND vortioxetine Adult, Senior Phase 2, 3, 4
74 studies found for:
("major depressive disorder" OR "major depression") AND duloxetine Adult, Senior Phase 2, 3, 4
Document: GreyLiterature.enl

ICTRP 04.06.2014

342 records for 243 trials found for: major depress* AND antidepress*
Document: ICTRP-040614.xlsx

Drugs@FDA 02.06.2014

Levomilnacipran:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=204168&DrugName=FETZIMA&ActiveIngred=LEVOMILNACIPRAN%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails
Vilazodone:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=022567&DrugName=VIIBRYD&ActiveIngred=VILAZODONE%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails
Vortioxetine:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=204447&DrugName=BRINTELLIX&ActiveIngred=VORTIOXETINE%20HYDROBROMIDE&SponsorApplicant=TAKEDA%20PHARMS%20USA&ProductMktStatus=1&goto=Search.DrugDetails
Folder: FDA

European Medicines Agency 02.06.2014

Levomilnacipran: 0
Vilazodone: 0
Vortioxetine:
http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/medicines/human/medicines/002717/human_med_001714.jsp&mid=WC0b01ac058001d124
Folder: EMA

National Institute of Mental Health website 11.06.2014

Search Terms: “major depression”, “major depressive disorder”
Folder: NIMH

American Psychological Association 11.06.2014

Search terms, “major depressive disorder”, major depression”
Folder: APA

Scopus 16.06.2014

(TITLE-ABS-KEY({major depressive disorder} OR {major depression}) OR KEY({disorder, major depressive})) AND (TITLE-ABS-KEY((bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine) OR ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy") OR (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort") OR ("s adenosyl l methionine" OR "S-Adenosylmethionine") OR ("omega 3") OR (acupuncture OR electroacupuncture) OR (yoga OR meditation OR mindfulness) OR ("physical activity" OR "physical exercise")) OR KEY(psychotherapy)) AND (TITLE-ABS-KEY(adult*)) AND (DOCTYPE(cp))

162 document results

Document: GreyLiterature.enl

Web of Science Conference Proceedings Citation Index- Science 16.06 2014

Set	Results	Search
		Indexes=CPCI-S Timespan=All years
# 1	3,944	TOPIC: ("major depressive disorder" OR "major depression")
		Indexes=CPCI-S Timespan=All years
# 2	4,014	TOPIC: (bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine)
		Indexes=CPCI-S Timespan=1990-2014
# 3	628	TOPIC: ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy")
		Indexes=CPCI-S Timespan=1990-2014
# 4	404	TOPIC: (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort")
		Indexes=CPCI-S Timespan=1990-2014
# 5	456	TOPIC: ("s adenosyl l methionine" OR "S-Adenosylmethionine")
		Indexes=CPCI-S Timespan=1990-2014
# 6	1,749	TOPIC: ("omega 3")
		Indexes=CPCI-S Timespan=1990-2014
# 7	1,068	TOPIC: (acupuncture OR electroacupuncture)
		Indexes=CPCI-S Timespan=1990-2014
# 8	517	TOPIC: (yoga OR meditation OR mindfulness)
		Indexes=CPCI-S Timespan=1990-2014
# 9	6,836	TOPIC: ("physical activity" OR "physical exercise")
		Indexes=CPCI-S Timespan=1990-2014
# 10	15,492	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
		Indexes=CPCI-S Timespan=1990-2014
# 11	874	#10 AND #1
		Indexes=CPCI-S Timespan=1990-2014
		Refined by: TOPIC: (adult*)
# 12	55	#10 AND #1

Document: GreyLiterature.enl

Appendix B. Cochrane Depression, Anxiety and Neurosis Group (CCDAN) Topic List: Intervention – Psychological Therapies[1]

- **Behavior therapy / behavior modification**
  - Activity scheduling
  - Assertiveness training [CINAHL]
  - Aversion therapy [APA]
    - Covert sensitization [APA]
  - Behavior contracting [CINAHL]
  - Behavior modification
  - Biofeedback, psychology [MeSH]
    - Feedback, sensory [MeSH]
  - Contingency management [CINAHL]
  - Conversion therapy [APA]
  - Distraction therapy
  - Exposure therapy (APA)
    - Abreaction therapy
    - Sensitivity training
    - Systematic desensitization therapy (APA)
      - Eye movement desensitization reprocessing [MeSH]
    - Implosive therapy [APA, MeSH]
  - Pleasant events
  - Psychoeducation
  - Problem-focused
  - Reciprocal inhibition therapy (APA)
  - Relaxation techniques [CINAHL]
  - Autogenic training
    - Distraction [CINAHL]
    - Guided imagery [CINAHL]
  - Response cost (APA)
  - Sleep phase chronotherapy [MeSH]
  - Social skills training
    - Social effectiveness
- **Cognitive behavioral therapy [APA]**
  - Problem solving
  - Rational emotive therapy
  - Reality therapy
  - Restructuring
  - Role play
  - Schemas

[1] Cochrane Depression, Anxiety, and Neurosis Group. CCDAN Topic List: Intervention - Psychological therapies. 2013 http://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf. Accessed October 17, 2014.

    - Self-control
    - Stress management
- **Third wave cognitive behavioral therapies**
    - Acceptance and commitment therapy (ACT)
    - Behavioral activation
    - Cognitive behavioral analysis system of psychotherapy (CBASP)
    - Compassion-focused
    - Dialectical behavior therapy (APA)
    - Diffusion
    - Functional analytic psychotherapy (FAP)
    - Metacognitive therapy
    - Mind training
    - Mindfulness
- **Psychodynamic therapies**
    - Brief psychotherapy
    - Countertransference
    - Freudian
    - Group therapy
        - Balint group therapy
    - Insight oriented therapy
    - Jungian
    - Kleinian
    - Object relations
    - Person centred therapy, client-centred therapy
    - Psychoanalytic therapy
        - Alderian therapy
        - Dream analysis
        - Free association
        - Self analysis
    - Short-term psychotherapy
    - Transference
- **Humanistic therapies**
    - Existential therapy
    - Experiential therapy
        - Process-experiential
        - Gestalt therapy
    - Expressive therapy
    - Griefwork
    - Rogerian
    - Non-directive therapy
    - Supportive therapy
    - Transactional analysis
- **Integrative therapies**
    - Cognitive analytical therapy
    - Counselling
    - Eclectic therapy

    - Interpersonal therapy
        - Psychodynamic interpersonal therapy
    - Multimodal
    - Transtheoretical
- **Systemic therapies**
    - Conjoint therapy
        - Couples, marital or relationship therapy
            - Emotion focused therapy
        - Family therapy
    - Integrative behavioral couple therapy (IBCT)
    - Narrative therapy
    - Personal construct
    - Socioenvironmental therapy
        - Milieu therapy
        - Therapeutic community
    - Solution focused brief therapy
- **Other psychologically-oriented interventions**
    - Acting out
    - Age regression therapy
    - Art therapy
    - Bibliotherapy
    - Catharsis
    - Colour therapy
    - Crisis intervention
    - Dance therapy
    - Drama therapy
    - Emotional freedom techniqueso hypnotherapy
        - Autosuggestion
        - Neuro-linguistic programming (NLP)
        - Persuasion
    - Meditation [CINAHL]
    - Morita therapy
    - Music therapy
    - Play therapy
    - Primal therapy
    - Psychodrama
    - Reminiscence therapy
    - Sex therapy

Appendix C. Studies Excluded at the Full-Text Review Stage

Exclude Code	Exclude Reason
X1	Ineligible publication type
X2	Ineligible population(s)
X3	Ineligible or no intervention(s)
X4	Ineligible study design
X5	Ineligible or no comparison(s)
X6	Ineligible outcome(s)
X7	Does not answer a Key Question of the review
X8	Mixed treatment comparisons
X9	Systematic review without relevant meta-analysis
X10	Abstract only available

1. St. John's wort ineffective for major depression. J Psychosoc Nurs Ment Health Serv. 2001;39(7):9-. Exclusion Code: X1
2. Research notebook. Study shows St. John's wort ineffective for major depression. FDA Consum. 2002;36(3):8-. Exclusion Code: X1
3. Treating late-life depression: pharmacotherapy or psychotherapy? Brown University Geriatric Psychopharmacology Update. 2006;10(12):3-4. Exclusion Code: X1
4. Paroxetine plus psychotherapy for major depression in the elderly. Brown University Psychopharmacology Update. 2006;17(8):4-5. Exclusion Code: X1
5. Paroxetine found to maintain quality of life in elderly patients with depression. Brown University Geriatric Psychopharmacology Update. 2007;11(11):1. Exclusion Code: X1
6. Augmenting standard antidepressant treatment may help recovery in elderly. Brown University Geriatric Psychopharmacology Update. 2007;11(8):1. Exclusion Code: X1
7. Cost effectiveness of therapy and fluoxetine for MDD in Romania... major depressive disorder. Brown University Psychopharmacology Update. 2009;20(4):4-. Exclusion Code: X1
8. Better response and remission with mirtazapine for MD... major depression. Brown University Psychopharmacology Update. 2010;21(10):3-4. PMID: 2010780944. Language: English. Entry Date: 20101008. Revision Date: 20140103. Publication Type: journal article. Journal Subset: Biomedical. Exclusion Code: X1
9. Omega-3 effective in treating major depression - but only in absence of anxiety. Canadian Nursing Home. 2010;21(3):26-. Exclusion Code: X1
10. [Therapy of moderately severe depressions in daily practice: first patient care research study reinforces clinical data]. MMW Fortschr Med. 2011 Oct 13;153(41):38-9. PMID: 22046838. Exclusion Code: X6
11. A Double-Blind, Paroxetine- and Placebo-Controlled Study of 50 mg/Day and 100 mg/Day of EB-1010 Among Outpatients With Major Depressive Disorder Who Have Responded Inadequately to Prior Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (Triple Reuptake Inhibitor Anti-Depressant Effects - TRIADE Study) [NCT01318434]. Clinicaltrials.gov [www.clinicaltrials.gov]; 2011. Exclusion Code: X9
12. . Mittelschwere und schwere depression: langzeitbehandlung mit hypericum-extrakt WS 5570 gleich wirksam wie paroxetin. Schweiz Z Ganzheits Medizin. 2008 May;20(4):198-9. PMID: 0110887. Exclusion Code: X1
13. Abt KL. The effects of a group exercise intervention in the adjunctive treatment of depression. US: ProQuest Information & Learning; 2006. Exclusion Code: X2
14. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient clinic: Clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. Int J Neuropsychopharmacol. 2003;6(1):41-9. Exclusion Code: X5

15. Alexopoulos GS, Canuso CM, Gharabawi GM, et al. Placebo-controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression. Am J Geriatr Psychiatry. 2008 Jan;16(1):21-30. PMID: 17928573. Exclusion Code: X5

16. Alper BS. Evidence-based medicine. St. John's wort may be as effective as standard antidepressants--and more tolerable--for major depression. Clinical Advisor for Nurse Practitioners. 2009;12(2):84-. PMID: 2010218029. Language: English. Entry Date: 20090410. Revision Date: 20090410. Publication Type: journal article. Exclusion Code: X1

17. Anghelescu IG, Kohnen R, Szegedi A, et al. Comparison of Hypericum extract WS 5570 and paroxetine in ongoing treatment after recovery from an episode of moderate to severe depression: results from a randomized multicenter study. Pharmacopsychiatry. 2006 Nov;39(6):213-9. PMID: 17124643. Exclusion Code: X2

18. Appelberg BG, Syvälahti EK, Koskinen TE, et al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry; 2001. p. 448-52. Exclusion Code: X5

19. Appelhof BC, Brouwer JP, van Dyck R, et al. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. J Clin Endocrinol Metab. 2004 Dec;89(12):6271-6. PMID: 15579788. Exclusion Code: X2

20. Arnow BA, Blasey C, Manber R, et al. Dropouts versus completers among chronically depressed outpatients. J Affect Disord. 2007 Jan;97(1-3):197-202. PMID: 16857266. Exclusion Code: X4

21. Arnow BA, Steidtmann D, Blasey C, et al. The relationship between the therapeutic alliance and treatment outcome in two distinct psychotherapies for chronic depression. J Consult Clin Psychol. 2013;81(4):627-38. PMID: 2013-01524-001. PMID: 23339536. First Author & Affiliation: Arnow, Bruce A. Exclusion Code: X2

22. Ashouri A, Atef-Vahid MK, Gharaee B, et al. Effectiveness of meta-cognitive and cognitive-behavioral therapy in patients with major depressive disorder. Iranian Journal of Psychiatry and Behavioral Sciences. 2013;7(2):24-34. Exclusion Code: X3

23. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: Maintenance of therapeutic benefit. In: Monat A, Lazarus RS, Reevy G, eds. The Praeger handbook on stress and coping. Vol. 2. Westport, CT: Praeger Publishers/Greenwood Publishing Group; 2007:529-40. Exclusion Code: X6

24. Bagby RM, Quilty LC, Segal ZV, et al. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. Can J Psychiatry. 2008 Jun;53(6):361-70. PMID: 18616856. Exclusion Code: X4

25. Baldomero EB, Ubago JG, Cercós CL, et al. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. Depress Anxiety. 2005;22(2):68-76. PMID: 2005-15269-004. PMID: 16094658. First Author & Affiliation: Baldomero, E. Baca. Exclusion Code: X3

26. Ballesteros J, Callado LF, Gutierrez M. An independent meta-analysis using summary data for clinical response, remission, and discontinuation for any reason from the 6 pivotal phase III randomized clinical trials of duloxetine in major depressive disorder. J Clin Psychopharmacol. 2007 Apr;27(2):219-21. PMID: 17414254. Exclusion Code: X5

27. Bauer M, Bschor T, Kunz D, et al. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry. 2000;157(9):1429-35. Exclusion Code: X2

28. Bauer M, Pretorius HW, Constant EL, et al. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009 Apr;70(4):540-9. PMID: 19358791. Exclusion Code: X3

29. Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: A clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol. 1996;16(4):307-14. PMID: 1996-05541-004. PMID: 8835706. Partial author list. First Author & Affiliation: Baumann, Pierre. Exclusion Code: X5

30. Bell AC, D'Zurilla TJ. Problem-solving therapy for depression: a meta-analysis. Clin Psychol Rev. 2009 Jun;29(4):348-53. PMID: 19299058. Exclusion Code: X2

31. Benazzi F. Fluoxetine and olanzapine for resistant depression. Am J Psychiatry. 2002 Jan;159(1):155-6. PMID: 11772722. Exclusion Code: X1

32. Benvenuti A, Rucci P, Miniati M, et al. Treatment-emergent mania/hypomania in unipolar patients. Bipolar Disord. 2008 Sep;10(6):726-32. PMID: 18837867. Exclusion Code: X2

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Appendix D. Risk of Bias Evaluations

Table D1. Risk of bias domains and ratings

Author, Year Trial Name	Randomization method adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care providers masked?	Patients masked?	High overall (i.e., ≥20%) attrition?	High differential (i.e., ≥15%) attrition?	Use Intention-to-treat analyses?	Appropriate method of handling dropouts in analyses used?	Could selective reporting of outcomes be an issue?	Risk of Bias
Barber et al., 2012[1]	Yes	NR	No	Unclear	No	No	Yes	Yes	Yes	Yes	No	Medium
Bastos et al., 2013[2]	NR	NR	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Medium
Behnke et al., 2002[3]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Yes	NR	Unclear	Medium
Bjerkenstedt et al., 2005[4]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Low
Blom et al., 2007[5]	NR	NR	Yes	Yes	Unclear	Unclear	Yes	No	Unclear	Unclear	No	Medium
Blumenthal et al., 1999[6] Babyak et al., 2000[7]	Unclear	Unclear	Unclear	Yes	Yes	No	Yes	No	Yes	Yes	No	Medium
Blumenthal et al, 2007[8] Hoffman et al., 2008[9]	Yes	Unclear	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Medium
Brenner et al., 2000[10]	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High
David et al., 2008[11] Sava et al., 2009[12]	NR	NR	Yes	Yes	No	No	No	No	Yes	Yes	No	Medium
Davidson et al., 2002[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Medium
Dekker et al., 2008[14]	NR	NR	Yes	NR	No	No	Yes	No	Yes	Yes	No	Medium
DeRubeis et al., 2005[15] Leykin et al., 2007[16]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	Medium

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomization method adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care providers masked?	Patients masked?	High overall (i.e., ≥20%) attrition?	High differential (i.e., ≥15%) attrition?	Use Intention-to-treat analyses?	Appropriate method of handling dropouts in analyses used?	Could selective reporting of outcomes be an issue?	Risk of Bias
Dimidjian et al., 2006[17]	NR	NR	Yes	NR	No	No	Yes	Yes	No	NR	No	High
Fava et al., 2005[18] Papakostas et al., 2007[19]	NR	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	High
Frank et al., 2011[20] Rucci, 2011[21]	NR	NR	No	Unclear	No	No	Yes	No	Yes	Yes	Yes	High
Gastpar et al., 2005[22]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium
Gastpar et al., 2006[23]	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Low
Gertsik et al., 2012[24]	NR	NR	Yes	NR	NR	Yes	Yes	Yes	No	NR	No	High
Harrer et al., 1999[25]	Yes	Unclear	Yes	Unclear	Unclear	Unclear	No	No	No	NR	Unclear	Medium
Hegerl et al., 2010[26]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	High
Huang et al., 2005[27]	Unclear	Unclear	Unclear	Unclear	No	No	No	No	No	No	No	Medium
Jazayeri et al., 2008[28]	NR	NR	Yes	Yes	Yes	Yes	Yes	No	No	No	No	High
Kennedy et al., 2007[29]	NR	NR	No	NR	No	No	Yes	No	No	NR	No	High
Lam et al., 2013[30]	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Low
Landenberger et al., 2002[31]	NR	NR	No	Yes	No	No	No	No	Yes	Yes	Unclear	Medium
Lenox-Smith and Jiang, 2008[32]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Low
McGrath et al., 2013[33]	Yes	Yes	No	Yes	No	No	Yes	No	No	NR	No	High

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomi-Zation Method Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline ?	Outcome Asse-ssors Masked?	Care Providers Masked?	Patients Masked?	High Overall (i.e., ≥20%) Attrition?	High Differential (i.e., ≥15%) Attrition?	Use Intention-to-Treat Analyses?	Appropriate Method of Handling Dropouts in Analyses Used?	Could Selective Reporting of Outcomes be an Issue?	Risk of Bias
Menchetti et al., 2014[34]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Medium
Miranda et al., 2003[35]	Yes	Yes	Yes	Yes	No	No	Unclear	No	Yes	Yes	No	Medium
WECare												
Mischoulon et al., 2014[36]	Yes	NR	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	No	High
Moradveisi et al., 2013[37]	Yes	NR	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	High
Moreno et al., 2006[38]	Unclear	Unclear	No	Unclear	Yes	Yes	No	No	No	Yes	Yes	High
Mynors-Wallis et al., 2000[39]	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes	Medium
Qu et al., 2013[40]	Yes	Unclear	Yes	Yes	No	No	No	No	No	NR	No	Medium
Chen et al., 2014[41]												
Raue et al., 2009[42]	NR	NR	NR	NR	No	No	No	NR	NR	NR	Yes	High
Salminen et al., 2008[43]	NR	NR	Yes	NR	No	No	Yes	No	Yes	NR	No	Medium
Kronstrom et al., 2009[44]												
Schrader et al., 2000[45]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	No	Medium
Segal et al., 2006[46]	NR	NR	Yes	NR	No	No	Yes	Yes	No	NR	No	High
Shamsaei et al., 2008[47]	Yes	NR	Yes	No	No	No	NR	NR	NR	NR	No	High
Song et al., 2007[48]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NR	Unclear	Yes	High
Sun et al., 2013[49]	Yes	Yes	Unclear	Unclear	No	Yes	No	No	Yes	No	No	High

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomi-Zation Method Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline ?	Outcome Asse-ssors Masked?	Care Providers Masked?	Patients Masked?	High Overall (i.e., ≥20%) Attrition?	High Differential (i.e., ≥15%) Attrition?	Use Intention-to-Treat Analyses?	Appropriate Method of Handling Dropouts in Analyses Used?	Could Selective Reporting of Outcomes be an Issue?	Risk of Bias
Szegedi et al., 2005[50]	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	No	Medium
Thase et al., 2007[51] Rush et al., 2006[52] Trivedi et al., 2006[53] STAR*D	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes	Yes	No	Medium
van Gurp et al., 2002[54]	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Medium
Zhang et al., 2009[55]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Medium

Appendix D References

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Appendix E: Summary of Findings Tables

KQ 1 and KQ4: Summary of Findings Tables

Table 1. Benefits of second-generation antidepressants compared with cognitive behavioral therapy monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with: HAM-D Followup: range 8 to 16 weeks	45 per 100	47 per 100 (40 to 55)	RR, 1.03 (0.87 to 1.21)	607 (5 trials)	Moderate [b]	Comparisons limited to fluoxetine, fluvoxamine, paroxetine, or sertraline and CBT, CT, PST, or REBT. Sensitivity analysis with 3 additional trials (rated high risk of bias) did not change the statistical significance of the results (RR, 1.09; 95% CI, 0.99 to 1.20).
Remission Assessed with: HAM-D Followup: range 12 to 16 weeks	49 per 100	59 per 100 (48 to 72)	RR, 1.19 (0.98 to 1.45)	379 (3 trials)	Low [b, c]	Comparisons limited to fluoxetine, fluvoxamine, or paroxetine and CBT, CT, PST, or REBT sensitivity analysis with 3 additional trials (rated high risk of bias) resulted in a statistically significant difference favoring SGA (RR, 1.19; 95% CI, 1.04 to 1.33).
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity Assessed with: Social Adjustment Scale Follow up: mean 12 weeks	Mean scores were within 0.3 points between groups and CIs overlapped.	Mean scores were within 0.3 points between groups and CIs overlapped.	Not estimable	116 (1 study)	Low [d, e]	Comparison limited to fluvoxamine or paroxetine and PST.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for inconsistency: inconsistent direction of point estimates.

[c] Downgraded for suspected selective outcome reporting bias.

[d] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[e] Downgraded for risk of bias: outcomes reporting bias; most trials did not report on functional capacity.

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; HAM-D = Hamilton Depression Rating Scale; NR: not reported; PST = problem solving therapy; REBT = rational emotive behavior therapy; RR = risk ratio; SGA = second-generation antidepressant

Table 2. Benefits of second-generation antidepressants compared with combinations of second-generation antidepressants and cognitive behavioral therapy

Outcomes	Anticipated absolute effects[a]: *Benefit with combination of SGA and CBT*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: MADRS or HAM-D Follow up: mean 12 weeks	68 per 100	70 per 100 (58 to 85)	RR, 1.03 (0.85 to 1.26)	174 (2 trials)	Low[b, c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.
Remission Assessed with: MADRS or HAM-D Follow up: mean 12 weeks	55 per 100	58 per 100 (45 to 76)	RR, 1.06 (0.82 to 1.38)	174 (2 trials)	Low[b, c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity Assessed with: Multiple scales Follow up: mean 12 weeks	Patients receiving the combination reported greater improvement on 3 of 5 work functioning measures compared with patients on SGA alone	Patients receiving the combination reported greater improvement on 3 of 5 work functioning measures compared with patients on SGA alone	Not estimable	170 (2 trials)	Low[b, c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for inconsistency: inconsistent direction of point estimates.

[c] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

CBT = cognitive behavioral therapy; CI = confidence interval; MADRS = Montgomery-Åsberg Depression Rating Scale; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 3. Benefits of second-generation antidepressants compared with integrative therapies monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit with integrative therapies alone*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up: mean 6 weeks	61 per 100	62 per 100 (53 to 75)	RR, 1.02 (0.86 to 1.22)	318 (1 trial)	Low[b, c]	Comparison limited to escitalopram and IPT.
Remission Assessed with: HAM-D Followup: range 8 to 12 weeks	50 per 100	46 per 100 (39 to 54)	RR, 0.92 (0.78 to 1.08)	605 (2 trials)	Low[d, e]	Comparison limited to citalopram, escitalopram, or sertraline and IPT. A third study (rated high risk of bias) reported no significant difference in effect but did not present rates of remission.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Downgraded for risk of bias: high risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.

[d] Downgraded for inconsistency: inconsistent direction of point estimates.

[e] Downgraded for risk of bias: one of the trials was rated high risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = Interpersonal Psychotherapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 4. Benefits of second-generation antidepressants compared with combinations of second-generation antidepressants and integrative therapies

Outcomes	Anticipated absolute effects[a]: *Benefit with combination of SGA and integrative therapies*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI) [a]	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission Assessed with: HAM-D Followup: range 8 to 12 weeks	NR	NR	OR, 3.22 (1.02 to 10.12)	97 (1 trial)	Low [b, c]	Comparison limited to nefazodone and combination of nefazodone and IPT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Further downgraded for imprecision (very wide confidence interval).

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 5. Benefits of second-generation antidepressants compared with psychodynamic therapies monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit or psychodynamic therapies alone*	Anticipated absolute effects[a] (95% CI): *Benefit or risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission assessed with: HAM-D followup: mean 16 weeks	46 per 100	48 per 100 (27 to 86)	RR, 1.04 (0.58 to 1.86)	51 (1 trial)	Low [b, c]	Comparison limited to fluoxetine.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	Few statistically significant differences in various scales. In one study, the proportion of patients on sick leave was higher in the SGA group than the PSYD group (12% vs. 4%, not significant),	Few statistically significant differences in various scales. In one study, the proportion of patients on sick leave was higher in the SGA group than the PSYD group (12% vs. 4%,not significant)	Not estimable	221 (2 trials)	Low [b, d]	Comparison limited to fluoxetine.

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Downgraded for risk of bias: outcomes reporting bias; most trials did not report on remission

[d] Downgraded for inconsistency: inconsistent direction of point estimates.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR = not reported; PSYD = psychodynamic therapy; RR = Risk ratio; SGA = second-generation antidepressant

Table 6. Benefits of second-generation antidepressants compared with combinations of second-generation antidepressants and psychodynamic therapies

Outcomes	Anticipated absolute effects[a]: *Benefit with integrative therapies alone*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	Effects on WAIS-III measures were similar for SGA and the combination of SGA and PSYD.	Effects on WAIS-III measures were similar for SGA and the combination of SGA and PSYD.	Not estimable	272 (1 trial)	Low [b, c]	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision (single study, small sample size, unable to estimate an overall effect).

[c] Further downgraded for imprecision (wide range of effects for various measures).

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 7. Benefits of second-generation antidepressants compared with third-wave cognitive behavioral therapy monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit with combination of SGA and third wave CBT*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up: mean 13 weeks	88 per 100	66 per 100 (53 to 83)	RR, 0.75 (0.6 to 0.94)	100 (1 trial)	Insufficient [b, c, d]	Comparison limited to sertraline.
Remission Assessed with: HAM-D Follow up: mean 13 weeks	82 per 100	48 per 100 (34 to 66)	RR, 0.59 (0.42 to 0.8)	100 (1 trial)	Insufficient [b, c, d]	Comparison limited to sertraline.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Downgraded for risk of bias: high overall and differential attrition not accounted for in reported effect size.

[d] Downgraded for risk of bias: suspected reporting bias.

CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR: Risk ratio; SGA = second-generation antidepressant

Table 8. Benefits of second-generation antidepressants compared with acupuncture monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit with Acupuncture*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D followup: mean 6 weeks	64 per 100	62 per 100 (50 to 77)	RR, 0.97 (0.78 to 1.21)	184 (2 trials)	Low[b, c]	Direct evidence limited to comparisons of fluoxetine vs acupuncture. Results consistent with NWMA comparisons to SGA medications (RR, 0.80, 95% CI, 0.46-1.40).
Remission Assessed with: HAM-D followup: mean 6 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for high risk of bias: high dropout; uncertainty about randomization and allocation concealment; no masking of outcome assessors

[c] Downgraded for imprecision: few events not meeting optimal information size (OIS)

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NWMA = network meta-analysis; RR: Risk ratio; SGA = second-generation antidepressant

Table 9. Benefits of second-generation antidepressants compared with combination of SGA and acupuncture

Outcomes	Anticipated Absolute Effects[a]: *Benefit with Combination of SGA and Acupuncture*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D followup: mean 6 weeks	71 per 100	52 per 100 (43 to 63)	RR, 0.73 (0.61 to 0.89)	288 (2 trials)	Low[b, c]	Direct evidence limited to two studies comparing either fluoxetine or paroxetine with acupuncture plus SGA.
Remission Assessed with: HAM-D followup: mean 6 weeks	28 per 100	23 per 100 (12 to 42)	RR, 0.83 (0.45 to 1.53)	157 (1 trial)	Low[b]	Direct evidence limited to a single trial of paroxetine with combined acupuncture plus paroxetine.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events

[c] Downgraded for inconsistency: large effect size differences between studies

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; RR: Risk ratio; SGA = second-generation antidepressant

Table 10. Benefits of second-generation antidepressants compared with omega-3 fatty acids monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit with Omega-3 Fatty Acids*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up: mean 8 weeks	45 per 100	40 per 100 (19 to 82)	RR, 0.5 (0.24 to 1.04)	NA, Network meta-analysis	Low[a b]	Direct evidence is limited to a comparison of fluoxetine with Omega-3 fatty acids. Results from network meta-analyses conflict with findings of the RCT and indicate greater efficacy of SGAs (RR, 2.00; 95% CI, 0.96 to 4.18) compared with Omega-3 fatty acids
Remission Assessed with: HAM-D Follow up: mean 8 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for indirectness: results are based on network meta-analyses

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; RR: Risk ratio; SGA = second-generation antidepressant

Table 11. Benefits of second-generation antidepressants compared with combination of SGA and omega-3 fatty acids

Outcomes	Anticipated Absolute Effects[a]: *Benefit with combination of SGA and Omega-3 Fatty Acids*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up mean 8 weeks	47 per 100	29 per 100 (16 to 54)	RR, 0.62 (0.33 to 1.14)	72 (2 trials)	Insufficient[b, c]	Direct evidence is limited to a comparison of fluoxetine with omega-3 fatty acids..
Remission Assessed with: HAM-D Follow up mean 8 weeks	44 per 100	18 per 100 (7 to 51)	RR, 0.41 (0.15 to 1.14)	42 (1 trial)	Insufficient[b, c]	Direct evidence is limited to a comparison of fluoxetine with omega-3 fatty acids.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for high risk of bias: high attrition and lack of ITT analysis

[c] Downgraded for imprecision: few events and confidence interval crosses threshold of appreciable difference

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; RR: Risk ratio; SGA = second-generation antidepressant

Table 12. Benefits of second-generation antidepressants compared with S-Adenosyl methionine monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit with combination of SGA and Integrative Therapy*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up mean 12 weeks	36 per 100	34 per 100 (21 to 54)	RR, 1.22 (0.66 to 2.27)	NA; results based on network meta-analyses	Low [b, c]	Direct evidence is limited to a single comparison of escitalopram with SAMe. Network meta-analyses found no statistically significant differences in response rates between SGA estimate: 1.22 (0.66, 2.27) compared with SAMe.
Remission Assessed with: HAM-D Follow up mean 12 weeks	28 per 100	28 per 100 (16 to 48)	RR, 0.98 (0.57 to 1.71)	129 (1 trial)	Insufficient [b, c]	Direct evidence is limited to a single comparison of escitalopram with SAMe.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: small study size

[c] Downgraded for indirectness: results are based on network meta-analyses

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR: Risk ratio; SAMe = S-Adenosylmethionine; SGA = second-generation antidepressant

Table 13. Benefits of second-generation antidepressants compared with St. John's wort monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit with St. John's Wort*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Follow up: range 4-12 weeks	57 per 100	55 per 100 (47 to 65)	RR, 0.97 (0.82 to 1.15)	1430 (8 trials)	Moderate[b]	Evidence is based on the comparison of SSRIs with SJW. Results from NWMA demonstrate reduced response rate with SGAs compared to SJW (RR, 0.82; 95% CI, 0.69 to 0.98).
Response in subgroup of older adults Assessed with: HAM-D Follow up: mean 6 weeks	65 per 100	68 per 100 (55 to 84)	RR, 1.05 (0.84 to 1.3)	161 (1 trial)	Low[c]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)
Remission Assessed with: HAM-D follow up: mean 13 weeks	25 per 100	21 per 100 (17 to 26)	RR, 0.83 (0.66 to 1.04)	683 (4 trials)	Moderate[d]	Evidence is based on the comparison of SSRIs with SJW.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for inconsistency: moderate heterogeneity (I-squared 56 percent)

[c] Downgraded for very serious imprecision

[d] Downgraded for imprecision: few events overall and confidence interval crosses threshold of appreciable difference

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; NWMA = network meta-analyses; RR: Risk ratio; SGA = second-generation antidepressant; SJW = St. John's wort; SSRI = selective serotonin reuptake inhibitor

Table 14. Benefits of second-generation antidepressants compared with exercise monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit with exercise*	Anticipated absolute effects[a] (95% CI) : *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D17 Follow up: mean 16 weeks	82 per 100	94 per 100 (41 to 217)	RR, 1.87 (0.81 to 4.33)[d]	Not estimable (network meta-analyses of RCTs)	Low [b, c]	Estimates based on network meta-analyses.
Remission Assessed with: HAM-D17 <8, no longer meeting criteria for MDD Follow up: mean 16 weeks	50 per 100	55 per 100 (44 to 70)	RR, 1.1 (0.87 to 1.39)[d]	254 (2 trials)	Moderate [b]	Comparison is limited to sertraline versus exercise.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events, confidence intervals cross threshold of appreciable difference

[c] Downgraded for indirectness: estimates are based on network meta-analyses

[d] Crude RR

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; NR = not reported; RR: Risk ratio; SGA = second-generation antidepressant

Table 15. Benefits of second-generation antidepressants compared with combination of second-generation antidepressants and exercise

Outcomes	Anticipated absolute effects[a]: *Benefit with combination of SGA and exercise*	Anticipated absolute effects[a] (95% CI) : *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NR	NR	Not estimable	0 (0 trial)	Insufficient	None
Remission Assessed with: HAM-D17 and no longer meeting criteria for MDD Follow up: mean 16 weeks	66 per 100	69 per 100 (52 to 90)	RR, 1.05 (0.8 to 1.03)[c]	103 (1 trial)	Low[b]	Comparison is limited to sertraline versus sertraline plus exercise.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events, confidence intervals cross threshold of appreciable difference

[c] Crude RR

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; NR = not reported; RR: Risk ratio; SGA = second-generation antidepressant

Table 16. Benefits of second-generation antidepressants compared with cognitive behavioral therapy as a function of severity

Outcomes	Anticipated absolute effects[a]: *Benefit with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients Assessed with: HAM-D Follow up: mean 16 weeks	56 per 100	40 per 100 (25 to 64)	RR, 0.72 (0.45 to 1.15)	82 (1 trial)	Insufficient[b, c]	Comparisons limited to paroxetine and CT.
Response to treatment for low severity patients Assessed with: HAM-D Follow up: mean 16 weeks	60 per 100	47 per 100 (29 to 75)	RR, 0.78 (0.48 to 1.25)	63 (1 trial)	Insufficient[b, c]	Comparisons limited to paroxetine and CT.
Remission in high severity patients Assessed with: HAM-D Follow up: mean 16 weeks	36 per 100	23 per 100 (11 to 46)	RR, 0.63 (0.31 to 1.29)	82 (1 trial)	Insufficient[b, c]	Comparisons limited to paroxetine and CT.
Remission in low severity patients Assessed with: HAM-D Follow up: mean 16 weeks	50 per 100	33 per 100 (18 to 60)	RR, 0.65 (0.35 to 1.2)	63 (1 trial)	Insufficient[b, c]	Comparisons limited to paroxetine and CT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded for imprecision: single study, small sample size, unable to estimate an effect.

[c] Downgraded for risk of bias: high attrition and small sample size

CI = confidence interval; CT, cognitive therapy; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 17. Benefits of second-generation antidepressants compared with integrative therapies as a function of severity

Outcomes	Anticipated absolute effects[a] (95% CI): *Benefit with integrative therapies monotherapy*	Anticipated absolute effects* (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients	NA	NA	NA	0 (0 trials)	Insufficient	None
Response to treatment for low severity patients	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission in high severity patients Assessed with: HAM-D Follow up: mean 8 weeks	45 per 100	40 per 100 (26 to 62)	RR, 0.89 (0.58 to 1.37)	111 (1 trial)	Insufficient[b, c]	Comparisons limited to sertraline or citalopram and IPT.
Remission in low severity patients Assessed with: HAM-D Follow up: mean 8 weeks	75 per 100	56 per 100 (43 to 71)	RR, 0.75 (0.58 to 0.96)	153 (1 trial)	Insufficient[b, c]	Comparisons limited to sertraline or citalopram and IPT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded for imprecision: single study, small sample size, unable to estimate an effect

[c] Downgraded for reporting bias: Selective non-reporting of several outcomes measured at 2 months, including Geriatric Depression Scale scores, QOL, and satisfaction.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 18. Benefits of second-generation antidepressants compared with third-wave cognitive behavioral therapy monotherapy as a function of severity

Outcomes	Anticipated absolute effects[a] (95% CI): *Benefit with third wave cognitive behavioral therapy monotherapy*	Anticipated absolute effects* (95% CI): *Benefit with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients Assessed with: HAM-D Follow up: mean 16 weeks	60 per 100	40 per 100 (26 to 63)	RR, 0.67 (0.43 to 1.05)	82 (1 trial)	Insufficient[b, c]	Comparison limited to paroxetine and BA.
Response to treatment for low severity patients Assessed with: HAM-D Follow up: mean 16 weeks	39 per 100	47 per 100 (24 to 90)	RR, 1.5 (0.62 to 2.32)	61 (1 trial)	Insufficient[b, c]	Comparison limited to paroxetine and BA.
Remission in high severity patients Assessed with: HAM-D Follow up: mean 16 weeks	36 per 100	17 per 100 (9 to 31)	RR, 0.47 (0.26 to 0.87)	82 (1 trial)	Insufficient[b, c]	Comparison limited to paroxetine and BA.
Remission in low severity patients Assessed with: HAM-D Follow up: mean 16 weeks	44 per 100	37 per 100 (18 to 76)	RR, 0.84 (0.41 to 1.72)	61 (1 trial)	Insufficient[b, c]	Comparison limited to paroxetine and BA.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	NR
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	NR

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded for imprecision; single study, small sample size, unable to estimate an effect

[c] Downgraded for risk of bias: high attrition

CI = confidence interval; BA = behavioral activation therapy; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 19. Benefits of second-generation antidepressants compared with SAMe as a function of baseline depressive severity

Outcomes	Anticipated Absolute Effects[a]): *Benefit with SAMe*	Anticipated Absolute Effects[a] (95% CI): *Benefit with SGA*	Impact of severity as an effect modifier	Number of Participants (Trials)	Strength of Evidence	Comments
Response – change in HAM-D score Assessed with: HAM-D Follow up mean 12 weeks	The mean change in HAM-D score in the control group was 6.19	The mean change in HAM-D score in the intervention group was 6.31 Absolute mean difference was 0.21 higher.	No statistically significant interaction between baseline HAM-D score and treatment groups for reduction in HAM-D scores over time (p=0.87).	129 (1 trial)	Insufficient [b, c]	Direct evidence is limited to a single study of SAMe versus escitalopram.
Remission	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for high risk of bias: high dropout

[c] Downgraded for imprecision: small sample size in a single study

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR: Risk ratio; SAMe = S-Adenosyl methionine; SGA = second-generation antidepressant

KQ 2: Summary of Findings Tables

Table 20. Benefits of SGA switches compared with other SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefits with other SGA switches*	Anticipated absolute effects[a] (95% CI): *Benefits with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with HAM-D-17 or QIDS-SR-16 Followup: 12 to 14 weeks	NA	NA	RR, 0.96 (0.71 to 1.30)[e, f]	727 (1 trial)	Moderate[b]	Comparisons limited to switch strategies to bupropion vs. sertraline.
	NA	NA	RR, 0.91 (0.68 to 1.22)[e, f]	727 (1 trial)	Moderate[b]	Comparisons limited to switch strategies to bupropion vs. venlafaxine.
	NA	NA	RR, 0.95 (0.71 to 1.26)[e, f]	727 (1 trial)	Moderate[b]	Comparisons limited to switch strategies: sertraline vs. venlafaxine.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup: 14 weeks	NR	NR	RR, 1.21 (0.84 to 1.75) [e, f]	727 (1 trial)	Low[c, d]	Comparisons limited to bupropion vs. sertraline vs. venlafaxine switch strategies. No statistically significant differences between any of the individual switch strategies regardless of the measure used.
Mean change in HAM-D score from baseline Followup: 14 weeks	63 per 100	57 per 100 (49 to 68)	RR, 0.91 (0.78 to 1.07)[f]	406 (1 trial)	Low[c, d]	Comparison limited to venlafaxine vs. citalopram switch strategies

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion; medication options not all maximized.

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for imprecision: few events reported.

e Relative Risk as reported in the article.

[f] Crude RR

CGI-S = ;CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; MADRS = :NR = not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 21. Benefits of SGA switches compared with nonpharmacologic switches for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefitswith nonpharmacologic switches*	Anticipated absolute effects[a] (95% CI): *Benefits with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup: 12 to 14 weeks	22 per 100	27 to 100 (13 to 54)	RR, 1.2 (0.6 to 2.43)[e]	122 (1 trial)[b]	Low[c, d]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup: 14 weeks	25 per 100	28 to 100 (15 to 54)	RR, 1.12 (0.58 to 2.16)[b, e]	122 (1 trial)[b]	Low[c, d]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.
Mean change in HAM-D score from baseline Followup:14 weeks	NR	NR	Not estimable	122 (1 trial)[b]	Low[c, d]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] QIDS-SR-16 remission rates led to similar conclusions as those measured by HAM-D-17: RR (95% CI) = 0.88 (0.48 to 1.60).

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for imprecision: single study.

[e] Crude RR

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NR = not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 22. Benefits of SGA augmentation compared with SGA augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefits with SGA aumentation*	Anticipated absolute effects[a] (95% CI): *Benefits with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup:14 weeks	27 per 100	32 to 100 (25 to 41)	RR, 1.18 (0.92 to 1.53)[e]	565 (1 trial)	Low[c, d]	Comparison limited to bupropion vs. buspirone augmentation of citalopram treatment.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup:14 weeks	30 per 100	30 to 100 (23 to 38)	RR, 0.99 (0.77 to 1.27)[b, e]	565 (1 trial)	Low[c, d]	Comparison limited to bupropion vs. buspirone augmentation of citalopram treatment
Mean change inQIDS-SR-16 score from baseline Followup:14 weeks	NR	NR	Not estimable	565 (1 trial)	Low[c, d]	Comparison limited to bupropion vs. buspirone augmentation of citalopram treatment.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] QIDS-SR-16 data did not affect conclusions about comparative remission rates: RR (95% CI) = 1.19 (0.95 to 1.48).

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for precision: few events reported.

[e] Crude RR

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NR = not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 23. Benefits of SGA augmentation compared with nonpharmacologic augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefits with nonpharma-cologic augmentation*	Anticipated absolute effects[a] (95% CI): *Benefits with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup: 14 weeks	35 per 100	28 to 100 (18 to 43)	RR, 0.8 (0.51 to 1.23)[e]	182 (1 trial)	Low[b, c]	Comparison limited to SGA (bupropion or buspirone) vs. CT augmentation of citalopram treatment.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup: 14 weeks	23 per 100	33 to 100 (20 to 56)	RR, 1.44 (0.87 to 2.41)[b, e]	182 (1 trial)	Low[b, c]	Comparison limited to SGA (bupropion or buspirone) vs. CT augmentation of citalopram treatment.
Mean change inQIDS-SR-16 score from baseline Followup: 14 weeks	NR	NR	Not estimable	182 (1 trial)	Low[b, c]	Comparison limited to SGA (bupropion or buspirone) vs. CT augmentation of citalopram treatment.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] QIDS-SR-16 data did not affect conclusions about comparative remission rates: RR (95% CI) = 1.08 (0.69 to 1.69).

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for imprecision: few events reported.

[e] Crude RR

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NR = not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 24. Benefit of SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt as a function of baseline severity

Outcomes	Anticipated absolute effects[a]: *Benefit with higher severity*	Anticipated absolute effects[a] (95% CI): *Benefit with lower severity*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response	NR	NR	Not estimable	0 (0 trials)	Insufficient	None
Remission Assessed with HAM-D-17 Followup: 12 to 14 weeks	NR	NR	Not estimable	(1 trials)[b]	Insufficient [c, d]	Comparisons limited to venlafaxine vs. citalopram switch strategies or to bupropion vs. sertraline vs. venlafaxine switch strategies.
Mean change inQIDS-SR-16 score from baseline	NR	NR	Not estimable	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Two secondary analyses of two different RCTs

c Downgraded for risk of bias: selective outcome reporting bias in one study

[d] Downgraded for inconsistency: two studies reported contrasting results

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NR = not reported; QIDS-SR-16 = ;RR = risk ratio; SGA = second-generation antidepressant

KQ 3 and KQ4: Summary of Findings Tables

Table 25. Risks of SGAs compared with CBT for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with CBT*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: range 8 to 16 weeks	1 per 100	2 per 100 (0 to 8)	RR, 1.2 (0.24 to 6.13)	465 (4 trials)[k]	Insufficient[f, h]	None
Serious adverse events Follow up: range 8 to 10 weeks	NR	NR	RR, 5.44 (0.31 to 96.36)	140 (2 trials)[k]	Insufficent[c, g, h]	None
Overall risk for overall adverse events: Follow up: mean 13 weeks	1 per 100	16 per 100 (2 to 122)	RR, 17.84 (2.32 to 137.4)	170 (1 trial)	Insufficient[b, d]	Results for SGAs appear to substantially underestimate the risk of adverse events. A comprehensive systematic assessments of the risk of harms for SGAs reported that, on average, 60 percent of patients treated with SGAs experience at least one adverse event during the course of treatment.
Overall discontinuation Follow up: range 8 to 14 weeks	17 per 100	14 per 100 (10 to 21)	RR, 0.85 (0.55 to 1.30)	560 (4 trials)[i]	Moderate[f]	Second-generation antidepressants are limited to fluoxetine, fluvoxamine, and paroxetine.
Discontinuation because of adverse events Follow up: range 8 to 14 weeks	2 per 100	8 per 100 (3 to 23)	RR, 2.00 (0.74 to 5.45)	388 (3 trials)[j]	Low[c,e]	Discontinuation rates because of adverse events were statistically significantly higher for patients on SGAs than on CBT when we included two high risk of bias studies (RR 3.09, 96% CI 1.14-8.35)

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence intervals wide.

[c] Not upgraded for large effect because of extreme imprecision.

[d] Downgraded for risk of bias: adverse events reported only for study completers.

[e] Downgraded for imprecision: very few events; 95% confidence intervals especially wide and cross both thresholds of appreciable differences

[f] Downgraded for imprecision: very few events

[g] Downgraded for risk of bias: one study's data for subset of patients with MDD not based on ITT analysis

[h] Downgraded for risk of bias: two of 4 studies had a high risk of bias due to high overall and differential attrition rates; in one study, attrition particularly high among SGA patients; in another study, available data based on completers analysis only

[i] Does not include data from 4 high risk of bias studies because sensitivity analysis including those studies did not change meta-analysis findings

[j] Does not include data from 2 high risk of bias studies because sensitivity analysis including those studies did not change meta-analysis findings

[k] Includes high risk of bias evidence because number of studies with lower risk of bias insufficient to allow meta-analysis of findings

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 26. Risks of SGAs compared with combinations of SGA and CBT for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with combination SGA and CBT*	Anticipated absolute effects[a] (95% CI): *Risk with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 16 weeks	16 per 100	12 per 100 (6 to 26)	RR, 0.77 (0.37 to 1.6)	176 (2 trials)	Low[b]	Comparison limited to escitalopram with escitalopram combined with telephone CBT
Discontinuation because of adverse events Follow up: mean 12 weeks	2 per 100	8 per 100 (2 to 37)	RR, 3.42 (0.73 to 16.01)	176 (2 trials)	Low[b, c]	Comparison limited to escitalopram with escitalopram combined with telephone CBT

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; very wide 95% confidence interval across both thresholds of appreciable differences.

[c] Not upgraded for large effect size because of extreme imprecision.

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 27. Risks of SGAs compared with integrative therapies for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with integrative therapies*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 12 weeks	16 per 100	6 per 100 (3 to 13)	RR, 0.39 (0.19 to 0.82)	291 (2 trials)	Insufficient[b, f]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	Comparison limited to escitalopram versus interpersonal therapy
Overall discontinuation Follow up: mean 13 weeks	11 per 100	16 per 100 (10 to 26)	RR, 1.38 (0.83 to 2.3)	384 (2 trials)	Insufficient[b, e]	Comparison limited to citalopram, nefazodone, and sertraline vs. Interpersonal therapy
Discontinuation because of adverse events Follow up: mean 13 weeks	NR	NR	RR, 0.33 (0.01 to 8.06)	287 (1 trial)	Insufficient[b, d]	Comparison limited to citalopram and sertraline versus interpersonal therapy

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events.

[c] Downgraded for risk of bias: high attrition rate; unclear whether outcome assessors were masked; in one study, no indication that suicidality incidence data adjusted for baseline presence of suicidality or that ITT analysis applied to suicidality data.

[d] Downgraded for risk of bias: outcomes reporting bias; most studies did not report on discontinuation because of adverse events

[e] Downgraded for risk of bias: one of two available studies did not report discontinuations taking place between randomization and onset of treatment; impossible to determine how unreported discontinuations would have affected our findings.

[f] Downgraded for imprecision: very few events in both studies, and in one study, 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 28. Risks of SGAs compared with combination of SGAs and integrative therapies for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with combination of SGAs and integrative therapies*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 16 weeks	25 per 100	27 per 100 (16 to 47)	RR, 1.11 (0.64 to 1.93)	96 (1 trial)	Insufficient[b, c]	Comparison limited to one trial of nefazodone with a combination of nefazodone and integrative therapy
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; very wide 95% confidence interval across both thresholds of appreciable differences.

[c] Not upgraded for large effect size because of extreme imprecision.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 29. Risks of SGAs compared with psychodynamic therapy for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with psychodynamic therapy*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 8 weeks	16 per 100	16 per 100 (7 to 34)	RR, 1.01 (0.47 to 2.09)	141 (1 trial)	Insufficient[b, e]	None
Suicidality Follow up: mean 96 weeks	3 per 100	4 per 100 (1 to 19)	RR, 1.32 (0.3 to 5.73)	181 (1 trial)	Low[b]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 16 weeks	25 per 100	17 per 100 (10 to 30)	RR, 0.68 (0.39 to 1.2)	192 (2 trials)	Insufficient[b, c, d]	Comparisons are limited to fluoxetine and venlafaxine vs. psychodynamic therapy
Overall discontinuation Follow up: mean 48 weeks	19 per 100	24 per 100 (9 to 69)	RR, 1.25 (0.44 to 3.57)	51 (1 trial)	Low[b]	None
Overall discontinuation Follow up: mean 96 weeks	19 per 100	15 per 100 (8 to 29)	RR, 0.81 (0.43 to 1.55)	181 (1 trial)	Low[b]	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence intervals cross both thresholds of appreciable differences.

[c] Downgraded for risk of bias: outcomes reporting bias in one of two available studies, in that attrition taking place between randomization and treatment onset left unreported.

[d] Downgraded for inconsistency: conflicting directionality of point estimates in the two available studies for overall discontinuation.

[e] Downgraded for risk of bias: high overall attrition and unclear how that attrition affected incidence rates of suicidality, despite use of modified ITT analysis.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 30. Risks of SGAs compared with combination of SGAs and psychodynamic therapy for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with combination of SGAs and psychodynamictherapy*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 96 weeks	1 per 100	4 per 100 (1 to 39)	RR, 4.00 (0.46 to 35.1)	182 (1 trial)	Low[b, c]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 96 weeks	32 per 100	15 per 100 (9 to 27)	RR, 0.48 (0.27 to 0.85)	182 (1 trial)	Low[b]	Comparison is limited to fluoxetine with a combination of fluoxetine and long-term psychodynamic therapy
Discontinuation because of adverse events	0 per 100	0 to 100 (0 to 0)	Not estimable	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecisions: very few events; confidence intervals crosses both thresholds of appreciable differences.

[c] Not upgraded for large effect because of extreme imprecision.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 31. Risks of SGA compared with third wave CBT for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with third wave CBT*	Anticipated absolute effects[a] (95% CI): *Risk with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 16 weeks	NA	NA	NA	143(1 trial)	Insufficient[b, c, f]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 13 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 13 weeks	10 per 100	27 per 100 (14 to 52)	RR, 2.76 (1.4 to 5.41)	243 (2 trials)	Insufficient[b, c, d]	None
Discontinuation because of adverse events Follow up: mean 13 weeks	3 per 100	23 per 100 (1 to 43)	RR, 7.00 (0.37 to 132.11)	243 (2 trials)	Insufficient[b, c, e]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence intervals wide

[c] Not upgraded for large effect because of extreme imprecision

[d] Downgraded for risk of bias: in one of 2 available studies, high differential attrition rate between SGA and third-wave CBT groups may have been affected by statistically significant difference in percentages of women assigned to each treatment

[e] Downgraded for imprecision: very few events; 95% confidence intervals very wide and cross both thresholds of appreciable differences

[f] Downgraded for risk of bias: in only available study reporting suicidality data, statistically significant baseline difference in percentages of women assigned to each treatment may have artificially affected risk of suicidality

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 32. Risks of SGAs compared with any psychological therapy for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with any psychological therapy*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: range 8 to 16 weeks	9 per 100	8 per 100 (4 to 17)	RR, 0.87 (0.42 to 1.77)	1227 (8 trials)	Low[fb, c]	None
Serious adverse events Follow up: mean 8 weeks	NR	NR	RR, 4.87 (0.27 to 87.69)	92 (1 trial)	Low[fb,?]	None
Overall risk for overall adverse events: Follow up: mean 14 weeks	1 per 100	16 per 100 (2 to 122)	RR, 17.84 (2.32 to 137.4)	170 (1 trial)	Insufficient[b, c]	None
Overall discontinuation Follow up: range 8 to 16 weeks	16 per 100	19 per 100 (15 to 23)	RR, 1.23 (0.79 to 1.91)	1679 (7 trials)	Moderate[b]	Interventions are limited to: 1) fluoxetine, fluvoxamine, paroxetine, sertraline, and 2) behavioral activation, cognitive therapy, problem solving therapy, rational emotive behavior therapy, short-term psychodynamic supportive psychotherapy
Discontinuation because of adverse events Follow up: range 8 to 16 weeks	2 per 100	7 per 100 (4 to 15)	RR, 2.64 (0.98 to 7.08)	1097 (7 trials)	Moderate[b]	Interventions are limited to: 1) fluoxetine, fluvoxamine, paroxetine, sertraline, and 2) behavioral activation, cognitive therapy, problem solving therapy, rational emotive

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events.

[c] Downgraded for risk of bias: very high attrition in two studies.

[d] Downgraded for risk of bias: adverse events reported only for study completers.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 33. Risks of SGAs compared with acupuncture for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with acupuncture*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for overall adverse events: direct evidence Follow up: mean 6 weeks	6 per 100	4 per 100 (1 to 24)	RR, 0.69 (0.12 to 3.98)	98 (1 trial)	Insufficient[f,,g]	None
Overall risk for overall adverse events: indirect evidence Follow up: mean 8 weeks	10 per 100	40 per 100 (35 to 47)	RR, 3.96 (3.4 to 4.62)	3128 (21 triala)	Moderate[b,]	A systematic review which did not meet our eligibility criteria because it also included other depressive disorders than MDD provides the most comprehensive assessment of the comparative risk of harms between SGAs and acupuncture
Overall discontinuation Follow up: mean 6 weeks	56 per 100	2 per 100 (0 to 31)	RR, 0.03 (0 to 0.56)	75 (1 trial)	Low[c,d,e]	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for indirectness: numbers are based on a systematic review that included all depressive disorders and some first generation antidepressants.

[c] Downgraded for imprecision: very few events; small sample size well below optimal information size.

[d] Not downgraded for risk of bias because lack of ITT analysis does not affect the validity of discontinuation outcomes.

[e] Not upgraded for large effect because of extreme imprecision.

[f] Downgraded for risk of bias: validity of data in question due to lack of reporting about key components of study design, including randomization, allocation concealment, between-group similarity of baseline characteristics, and use of blinded outcome assessment.

[g] Downgraded for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 34. Risks of SGAs compared with combination of SGAs and acupuncture for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with combination of SGA and acupuncture*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 8 weeks	NR	NR	Not estimable	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 8 weeks	4 per 100	4 per 100 (1 to 21)	RR, 1.00 (0.21 to 4.79)	140 (1 trial)	Low[b]	None
Overall discontinuation Follow up: mean 6 weeks	10 per 100	13 per 100 (5 to 31)	RR, 1.29 (0.53 to 3.14)	428 (3 trials)	Moderate[c]	None
Discontinuation because of adverse events Follow up: mean 6 weeks	2 per 100	1 per 100 (0 to 7)	RR, 0.37 (0.04 to 3.54)	288 (2 trials)	Low[b]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

[c] Downgraded for imprecision: few events; 95% confidence interval nearly crosses both thresholds of appreciable differences; not downgraded any further because overall sample size exceeds optimal information size of 300.

[d] Crude RR

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 35. Risks of SGAs compared with omega-3 fatty acids for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with omega-3 fatty acids*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 8 weeks	5 per 100	2 per 100 (0 to 39)	RR, 0.33 (0.01 to 7.72)	40 (1 trial)	Insufficient[b, c]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 4 weeks	15 per 100	15 per 100 (4 to 66)	RR, 1.0 (0.23 to 4.37)	40 (1 trial)	Low[b]	None
Discontinuation because of adverse events Follow up: mean 8 weeks	5 per 100	5 per 100 (0 to 75)	RR, 1.0 (0.07 to 14.9)	40 (1 trial)	Low[b]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence intervals cross both thresholds of appreciable differences.

[c] Downgraded for risk of bias: high drop out rates, no intention-to-treat analyses available.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 36. Risks of SGAs compared with combination of SGAs and omega-3 fatty acids for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with combination of SGAs and omega-3 fatty acids*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 4 weeks	10 per 100	24 per 100 (8 to 70)	RR, 2.38 (0.81 to 6.98)	82 (2 trials)	Low[c, d]	Overall discontinuation rates were also similar between fluoxetine and a combination of fluoxetine and omega-3 fatty acids
Discontinuation because of adverse events Follow up: mean 8 weeks	10 per 100	5 per 100 (.5 to 51)	RR, 0.05 (0.05 to 508)	40 (1 trial)	Low[b]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

[c] Not upgraded for large effect because of imprecision

[d] Downgraded for imprecision: very few events; 95% confidence intervals nearly cross both thresholds of appreciable differences.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 37. Risks of SGAs compared with SAMe for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with SAMe*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality Follow up: mean 8 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	No information on overall risk of adverse events. One study provided data about selected adverse events only.
Overall discontinuation Follow up: mean 12 weeks	44 per 100	52 per 100 (34 to 79)	RR, 1.19 (0.78 to 1.8)	129 (1 trial)	Low[d]	None
Discontinuation because of adverse events Follow up: mean 12 weeks	5 per 100	12 per 100 (3 to 44)	RR, 2.63 (073 to 9.46)	129 (1 trial)	Insufficent[b, c]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events; 95% confidence interval crosses both thresholds of appreciable differences.

[c] Downgraded for risk of bias: very high overall drop out rate.

[d] Downgraded for imprecision: few events; 95% confidence interval crosses nearly both thresholds of appreciable differences

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 38. Risks of SGAs compared with St. John's wort for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with St. John's wort*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	1 per 100	1 per 100 (0 to 10)	RR, 1.03 (0.07 to 16.34)	331 (3 trials)	Insufficent[j, k]	None
Serious adverse events	2 per 100	1 per 100 (0 to 3)	RR, 0.63 (0.21 to 1.93)	932 (5 trials)	Low[f, g]	None
Risk for overall adverse events	39 per 100	47 per 100 (41 to 53)	RR, 1.19 (1.05 to 1.34)	1427 (8 trials)	Moderate[d, e]	None
Risk for overall adverse events In subgroup based ol older age	65 per 100	84 [rt 100	RR, 1.30 (0.66 to 2.54)	131 (1 trial)	Low [l]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)
Overall discontinuation	14 per 100	18 per 100 14 to 22)	RR, 1.29 (1.04 to 1.6)	1813 (12 trials)	Moderate[b, c]	None
Discontinuation because of adverse events	4 per 100	7 per 100 (5 to 10)	RR, 1.79 (1.19 to 2.71)	1773 (11 trials)	Moderate[h, i]	Crude RR
Discontinuation because of adverse events in subgroup based on older age	65 per 100	79 per 100 (29 to 218)	RR, 1.22 (0.44 to 3.36)	161 (1 trial)	Low [l]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Three of 12 included trials were rated as having a high risk of bias because of how they reported harms data, including overall discontinuation. In addition, one study with a low risk of bias rating reported conflicting discontinuation data, making it unclear which of its data were accurate. Still, sensitivity analysis results no different than primary analysis.

[c] <300 events overall (N=281), and summary point estimate non-significant, but 95% CI crosses the 1.25 threshold.

[d] Substantial heterogeneity (I-squared = 65%) in the directionality of point estimates, although all but two trials' 95% CIs overlapped. Specifically, three of 8 included trials found that patients taking SJW experienced fewer overall adverse events, in contrast to what the other five trials found.

[e] Summary point estimate non-significant, and its 95% CI crosses the 1.25 threshold.

[f] Summary point estimate non-significant, but its 95% CI crosses both the 0.75 and 1.25 thresholds. Also, far fewer than 300 events overall (N=13).

[g] One of five included trials was rated as having a high risk of bias.

[h] Two of 11 included trials were rated as having a high risk of bias.

[i] <300 events overall (N=94).

[j] Only 2 events overall, 1 per relevant study.

[k] Conflicting evidence and no clear pattern emerging because only one case of suicidality in each treatment group.

[l]Downgraded for serious imprecision; does not fulfill OIS, small number of events

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 39. Risks of SGAs compared with exercise for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with exercise*	Anticipated absolute effects[a] (95% CI): *Risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 16 weeks	2 per 100	1 per 100 (1 to 3)	RR, 0.87 (0.48 to 1.59)	254 (2 trials)	Low[b]	None
Discontinuation because of adverse events Follow up: mean 16 weeks	NR	NR	RR, 20.96 (1.19 to 367.97)	254 (2 trials)	Low[c, d]	Comparison limited to sertraline vs. exercise. Patients treated with a combination of sertraline and exercise had similar discontinuation rates because of adverse events as patients on sertraline monotherapy (9% vs. 10%).

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events; confidence interval crosses threshold of appreciable difference.

[c] Downgraded for imprecision: very few events; very wide confidence interval.

[d] Not upgraded for large effect size because of extreme imprecision.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 40. Risks of SGAs compared with combination of SGA and exercise for MDD in adults

Outcomes	Anticipated absolute effects[a]: Risk with SGA and exercise	Anticipated absolute effects[a] (95% CI): Risk with SGAs	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Follow up: mean 16 weeks	20 per 100	15 per 100 (6 to 35)	RR, 0.73 (0.31 to 1.73)	103 (1 trial)	Low[b]	None
Discontinuation because of adverse events Follow up: mean 16 weeks	9 per 100	10 per 100 (3 to 34)	RR, 1.15 (0.35 to 3.72)	103 (1 trial)	Low[b]	Comparison limited to sertraline vs. Sertraline + exercise

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: very few events; very wide 95% confidence interval across both thresholds of appreciable differences.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table 41. Risks of SGA switches compared with other SGA switches for MDD in adults

Outcomes	Anticipated absolute effects[a]: *Risk with other SGA switches*	Anticipated absolute effects[a] (95% CI): *Risk with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Suicidality	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Follow up: mean 12 weeks	63 per 100	57 per 100 (49 to 68)	RR, 0.91 (0.78 to 1.07)	406 (1 trial)	Low[b,c]	Comparison limited to switch to venlafaxine vs. switch to citalopram
Overall discontinuation Follow up: mean 12 weeks	21 per 100	24 per 100 (17 to 35)	RR, 1.17 (0.82 to 1.68)	406 (1 trial)	Low[b,c]	Comparison limited to switch to venlafaxine vs. switch to citalopram
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: small number of events.

[c] Downgraded for risk of bias: potential confounding from prior treatment attempts with psychotherapy, which was not accounted for at baseline.

CI = confidence interval; CT = cognitive therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Appendix F. Studies Included in Network Meta-Analyses

1. Institute for Quality and Efficiency in Health Care (IQWiG). Selektive Serotonin und Noradrenalin Wiederaufnahmehemmer (SNRI) bie Patienten mit Depressionen, A05-20A, Version 1.0. Institute for Quality and Efficiency in Health Care (IQWiG) (c) IQWiG (Institute for Quality and Efficiency in Health Care). Cologne, Germany: 2009.
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4. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol. 2012 Jun;15(5):589-600. Epub: 2011/07/20. PMID: 21767441.
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12. Bjerkenstedt L, Edman GV, Alken RG, et al. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-7. Epub: 2004/11/13. PMID: 15538592.
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44. GmbH WP. Randomized, double-blind comparison of venlafaxine (WY-45, 030), imipramine, and placebo capsules in outpatients with major depression: study 600A-303-US-303-EXT-GMR-20448.

45. GmbH WP. A randomized double-blind comparision of venlafaxine XR and paroxetine in outpatients with moderate to severe major depression: study 0600-428-IT-SDC-3993.

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